REMARKS

Status of the Application and the Present Amendment

Claims 2-5 and 15-27 are pending and stand rejected in the application. With entry of the present amendment, claims 2, 15, 19, and 20 have been amended. The claim amendments are made to correct typographical error, or to improve clarity or consistency of claim language. In addition, the specification has been amended to update priority information, and the tile has been amended to be more descriptive of the presently claimed invention. Applicants note that no new matter has been added by the present amendments and submissions.

The following remarks address issues raised in the Office Action.

Information Disclosure Statement

The Office Action stated that pages 1 and 2 of the Form PTO-1449 submitted with the Information Disclosure Statement in February 2002 were missing. In response, Applicants enclose copies of all pages of the noted PTO-1449 form. It is respectfully requested that the references cited on the form be considered by the Examiner.

Priority Date of the Subject Application

It was noted in the Office Action that the immediate parent of the subject application, application serial number 08/648,810 (the '810 application; filed May 6, 1996), is a continuation-in-part, not a continuation, of parent application serial number 07/846,208 (the '208 application; filed March 4, 1992). The Examiner also stated that "instant case is afforded the filing date of the parent case."

In response, Applicants acknowledged that the '810 application is indeed a continuation-in-part of the '208 application. The subject specification has been corrected accordingly, as suggested by the Examiner. However, it is not clear what is meant by the statement in the Office Action that "instant case is afforded the filing date" of the '810 application (i.e., May 6, 1996). Applicants note that while the '810 application is a CIP, not a continuation, of the '208 application, it does not follow that the subject application does not

have the earliest priority date of March 4, 1992, the filing date of the '208 application. Rather, it is readily clear that claims of the instant application can have a priority date of March 4, 1992 if the specific subject matter claimed was disclosed in the '208 application as filed on March 4, 1992. Only claims which find support in the '810 application, but not in the '208 application, will have a priority date of May 6, 1996.

Title of the Subject Invention

The Office Action alleged that the title of the subject invention is not descriptive. Applicants have amended the title herewith to be more clearly indicative of the presently claimed invention.

Rejection Under 35 U.S.C. 112, 1st Paragraph

Claims 20-27 were objected to as allegedly not enabled. The Examiner acknowledged that independent claim 15 is enabled. However, the Examiner stated that the specification does not provide enablement for dependent claims 20-27. It was alleged that the specification does not disclose a method of suppressing a response which accompanies tissue transplantation by administering IL-10 and an antigen or anti-CD3 antibody. The Examiner stated that the specification does not present any data that administration of IL-10 with an antigen or with anti-CD3 antibodies indeed suppresses a response which accompanies tissue transplantation. This rejection is respectfully traversed for the reasons stated below.

First of all, Applicants note that claims 25-27 do not depend from claim 15 and do not recite inhibiting or suppressing a response which "accompanies tissue transplantation." Similarly, claim 24 also does not recite suppressing a response which accompanies tissue transplantation. Applicants assume that claims 24-27 were inadvertently included in the instant rejection. Accordingly, the following remarks are directed to the instant rejection to the extent that it is applied to claims 20-23. However, if the Examiner maintains the rejection of claims 24-27 as non-enabled, Applicants respectfully request clarification.

The rejection of claims 20-23 is predicated on the assertion that the specification did not disclose actual data demonstrating suppression of an immune response which accompanies tissue transplantation. In response, Applicants note that what is exemplified in a patent application does not equate with teachings of the disclosures of the invention. It is well established that an applicant should not be limited to the specific embodiments identified in the specification when other operable embodiments may be discovered with only routine experimentation using the teaching of the specification. *In re Goffe*, 191 USPQ 429, 431 (CCPA 1976). To insist that the claims encompass only what has been experimentally demonstrated is plainly improper.

In addition, contrary to the assertions in the Office Action, the subject specification and the '208 specification both provided experimental evidence that IL-10 can play an important role in T cell proliferative response in stem cell transplantation. For example, Example 7 of the subject specification (Example 5 of the '208 specification) disclosed human patients with severe combined immunodeficiency (SCID) who were transplanted with fetal liver stem cells. The data indicate that exogenous IL-10 significantly suppressed the proliferative responses of CD4+ host-reactive T cell clones in vitro and that IL-10 production by host-reactive T cells may play an important role in down-regulating their responses in vivo (see, e.g., page 46, lines 19-23). Such disclosures simply provide further specific evidence that the method recited in claim 15 is enabled when the response to be suppressed accompanies tissue transplantation.

Further, claims 20-23 should be distinguished from a claim which recites a further step of "inhibiting tissue rejection" in addition to suppressing antigen-specific T cell response by administering IL-10 and the antigen. In the latter case, there may be a different question whether suppressing T cell response would indeed lead to inhibition of tissue rejection. By contrast, claims 20-23, which depend from independent claim 15, merely specify that the immune response recited in claim 15 accompanies tissue transplantation. These claims do not add additional steps or procedures to claim 15 that might otherwise call into question whether the additional steps or procedures are enabled. Rather, they merely recite a further

parameter (i.e., narrowing) of the broader subject matter of claim 15 that was already indicated by the Examiner as enabled. By way of analogy, if a broad claim directed to treating insomnia of dogs is enabled, then a dependent claim is surely also enabled if the only additional claim feature is to specify that the dog is German shepherd or is pregnant. Enablement of the dependent claim may become an issue only if additional steps or procedures are added, e.g., inducing birth from the pregnant dog while being treated for insomnia.

For all the reasons stated above, Applicants submit that claims 20-23, as well as claims 24-27, are enabled. The instant rejection should therefore be withdrawn.

Rejection Under 35 U.S.C. 112, 2nd Paragraph

The Office Action made a number of rejections of the pending claims based on alleged indefiniteness. Each of the rejections is addressed below. As an initial matter, Applicants note that an indefiniteness rejection should not be based on reading the claim language in abstract. Rather, as stated in the MPEP:

> Definiteness of claim language must be analyzed, not in a vacuum, but in light of:
> (A) The content of the particular application disclosure;
> (B) The teachings of the prior art; and
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. [MPEP § 2173.02 at 2100-194]

Claim 2 was rejected as allegedly vague and indefinite. The Examiner stated that it is not clear what is being claimed. Although Applicants respectfully traverse the rejection, to expedite prosecution of the subject application, Applicants have amended claim 2. The amended claim now makes abundantly clear that the claimed method is directed to inhibiting an antigen-specific response of an immune system by administration of IL-10 and an antigen.

Claim 3(b) was also rejected as vague and definite in the recital of "proliferative response of CD4+ host reactive T cell." Applicants respectfully traverse. As noted above,

claim language must be analyzed in light of disclosure of the subject application and teachings of the relevant art. In connection with discussions of stem cell transplantation, the subject specification disclosed that proliferation of host-reactive donor CD4+ T cells was inhibited by exogenous IL-10 (see, e.g., page 45, lines 17-31; and page 47, lines 2-9). Based on the subject disclosure, one of ordinary skill in the art would readily understand that the noted phrase refers to proliferation of the CD4+ T cells as opposed to proliferation of other cells.

Claim 2 is directed to inhibiting an antigen-specific response of an immune system (i.e., in vivo activity). Claim 3(b) depends from claim 2 and further specifies that the method inhibits proliferation of host-reactive CD4+ T cells. Thus, upon reviewing the subject disclosure, one would also appreciate that inhibition of proliferation of the CD4+ cells recited in the claim also relates to in vivo activities (as opposed to in a tissue culture) due to administration of IL-10. Accordingly, Applicants submit that there is no indefiniteness in claim 3(b) and request that the rejection be withdrawn. Should this rejection be maintained, Applicants respectfully request clarification from the Examiner in order to better address the issue.

Claim 3(c) was rejected on the ground that it is unclear whether "said inhibiting" refers to the "inhibiting" recited in claim 2 or to the "inhibiting" recited in claim 3(b). In response, Applicants note that claim 3(b) and 3(c) were recited as alternative members of a Markush group, and that elements recited in one member (3(c)) cannot limit another member (3(b)). Therefore, "said inhibiting" recited in 3(c) can only refer to the "inhibiting" recited in claim 2.

Claim 4 was rejected because the meaning of "responder T cell activation" is not clear to the Examiner. In response, Applicants again note that claim language must be interpreted in view of subject disclosure and knowledge well know in the relevant art. T cell activation has its ordinary meaning that is readily understood by one of skill in the art. The specification has provided abundant teachings of the inhibitory effect of IL-10 on T cell activation (see, e.g., at page 11, lines 26-27; and page 58, lines 11-12). Similarly, simulator cell and responder cell are terms well known and routinely used in the art of immunology,

especially in the context of immune proliferation assays. The subject specification also provided extensive discussions of using various stimulators to determine effect of IL-10 on proliferation of responder T cells (see, e.g., at page 21, line 31 to page 22, line 5; page 41, lines 19-21; and page 43, lines 1-2). It is respectfully submitted that there is no indefiniteness in the recital of "responder T cell activation" in claim 4.

Claim 5 was rejected as allegedly unclear. Again, Applicants note that the subject specification makes clear that the inhibitory effect of IL-10 on T cell activation is not only due to its cytokine inhibitory activity, but also due to reduced capacity of PBMC, monocytes, and normal B cells in stimulating the T cells (see, e.g., page 43, lines 11-19). Thus, claim 5 simply specifies that administration of IL-10 also leads to reduced stimulatory activity of the recited cells (e.g., PBMC or monocytes) on T cell activation.

Claim 15 was rejected as allegedly indefinite. In response, Applicants have amended the claim to make it clear that the method is directed to suppressing an immune response of a T cell to an antigen by administration of IL-10 and the antigen or an anti-CD3 antibody. Accordingly, Applicants submit there is no indefiniteness in the claim as amended.

In response to rejection of claim 19, Applicants have amended the claim to make it clear that response of the T cell to subsequent stimulation with the antigen is also suppressed. The subject specification has provided teachings that IL-10 induced antigen-specific anergy also reflects the inability of these antigen-specific cells to respond to subsequent restimulation with the specific antigen (see, page 19, lines 8-14).

Claims 20 and 23 were also rejected as allegedly indefinite. In response, claim 20 has been amended to clarify the response to subsequent stimulation accompanies tissue transplantation. This response of the T cell is due to stimulation of an alloantigen on a tissue that is to be transplanted. The subject specification (e.g., at page 5, lines 1-9) disclosed that in tissue transplantation, it is necessary to suppress immune response of the host to the donor tissue. For example, T cells from the recipient can be treated with an antigen from the donor MHC and IL-10 prior to the tissue transplantation. The treated T cells are introduced into the recipient. As a result, response to subsequent stimulation when the tissue is transplanted is

suppressed. Alternatively, IL-10 is administered to the tissue to be transplanted before the transplantation. In any event, the purpose is to induce antigen-specific anergy of T cell in the recipient so that there will be no adverse immune response when the tissue is transplanted. The anergy can be induced in vitro or in vivo. If performed in vitro, the treated T cells need to be introduced into the recipient.

In light of the above claim amendments and remarks, Applicants submit that there is no indefiniteness in the presently pending claims. The instant rejections should therefore be withdrawn.

Rejection Under 35 U.S.C. 102

Claims 2-5 and 15-19 were rejected as allegedly anticipated by Rott et al. (Eur. J. Immunol. 24:1434-1440, 1994). It was stated in the Office Action that Rott et al. disclosed a methods of inhibiting subsequent induction of EAE by administering IL-10 with myelin basic protein and therefor anticipated the instant claims. Applicants respectfully traverse this rejection.

The present invention is not anticipated by Rott et al. because Rott et al. do not teach or suggest each and every element of the instant claims. Nevertheless, without getting into a detailed analysis of the disclosure of Rott et al., Applicants note that Rott et al. is not an appropriate reference to be cited against the present invention. As discussed above, the present application has an earliest priority date of March 4, 1992 (the filing date of the '208 application). While not all disclosures of the subject specification were present in the '208 application, the presently claimed invention is fully disclosed and supported in the '208 specification. Description of inhibiting an antigen-specific response by administering IL-10 and the antigen, as presently claimed in independent claims 2, 15, 25, and 27, is replete in the '208 specification. Applicants attach a copy of the substitute specification filed in the '208 application in May 1992. Support for the present independent claims is provided at, e.g., page 9, line 36 to page 10, line 5; and pages 20-25 (Example 4). Other elements recited in

dependent claims 3-5, 16-24, and 26 are also supported in the '208 specification, e.g., at pages 4-5; pages 8-11; and the Examples.

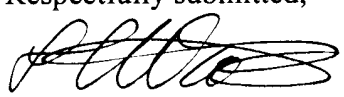
Thus, the '208 application has disclosed and enabled the presently claimed invention. Accordingly, the present claims have priority date at least as early as March 4, 1992. On the other hand, Rott et al. was not published until 1994. For this reason alone, the Rott et al. publication is not a reference that can be properly cited against the subject application and does not anticipate the present claims. Accordingly, the instant rejection must be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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Attachments: Appendix: Clean version of amendments;
Copy of IDS and Form PTO-1449 submitted January 28, 2002;
Copy of substitute specification filed in USSN 07/846,208 in May 1992

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Appendix: Clean Version Of Amendments

I. Amendments to the Specification

The first paragraph at page 1, lines 5-7 has been amended as follows.

-- The present Application is a divisional of and claims priority to application serial number 08/643,810, filed May 6, 1996, now Patent No. 6,277,635, which is a continuation-in-part of commonly assigned U.S.S.N. 07/846,208, filed March 4, 1992, now abandoned. Each of these earlier filed applications is incorporated herein by reference and for all purposes.

II. Amendments to the Claims (claims unamended herewith appear in small font)

2. A method of inhibiting an antigen-specific response of an immune system to subsequent presentation of said antigen, comprising administering to said immune system an effective amount of exogenous interleukin-10 and said antigen.

3. The method of Claim 2:

a) wherein said immune response is mediated by a macrophage, APC, langerhans cell, or dendritic cell;

b) further inhibiting proliferative response of CD4+ host-reactive T cell clones; or

c) wherein said inhibiting persists for at least about 21 days.

4. The method of Claim 2, wherein said effective amount is sufficient to decrease responder T cell activation.

5. The method of Claim 4, further comprising reduced stimulatory capacity of peripheral blood mononuclear cells, dendritic cells, monocytes, and/or normal B cells.

15. (Amended) A method of suppressing an immune response of a T cell to an antigen, comprising administering to said cell a combination of:

a) IL-10; and

b) either said antigen or anti-CD3 antibodies.

16. The method of Claim 15, wherein said antigen is alloantigen or self antigen.

17. The method of Claim 16, wherein said antigen is restricted by MHC molecules.

18. The method of Claim 15, performed in vivo.

19. (Amended) The method of Claim 15, which further comprising suppressing response to subsequent stimulation to said T cell with said antigen.

20. (Amended) The method of Claim 19, wherein said response to subsequent stimulation accompanies tissue transplantation.

21. The method of Claim 20, wherein said tissue is an organ or bone marrow.

22. The method of Claim 20, wherein said T cell is from the recipient of said tissue transplantation.

23. The method of Claim 15, wherein said response accompanies tissue transplantation and:

a) said administering is prior to said tissue transplantation;

b) said T cell is introduced to the recipient of said tissue transplantation; or

c) IL-10 is administered to the tissue to be transplanted before said transplantation.

24. The method of Claim 16, wherein said antigen causes an autoimmune disease.

25. A method of suppressing a subsequent response in a T cell to an antigen, comprising administering to an immune system comprising said cell with a combination of:

a) exogenous IL-10; and

b) either antigen or anti-CD3 antibodies.

26. The method of Claim 25, wherein said IL-10 is administered for at least about 7 days.

27. A method of inducing in a T cell anergy to an MHC antigen, comprising administering to a precurser to said T cell:

a) exogenous IL-10 and said antigen; or

b) exogenous IL-10 with anti-CD3.